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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/779,560	02/09/2001	Marianne Harboe	58982.000002	6162

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 12/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/779,560	HARBOE, MARIANNE	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,6,9-14,16-18,29-31,35,36,39,42 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6,9-14,16-18,29-31,35,36,39,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/31/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 5-6, 9-14, 16-18, 35-36, 39, and 42-43 are pending in the application.

[2] Applicant's amendment to the claims, filed on 31 October 2006, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims in accordance with 37 CFR 1.121(c).

[3] Receipt of an information disclosure statement, filed 31 October 2006, is acknowledged.

[4] Applicant's arguments filed on 31 October 2006 in response to the Office action mailed 31 May 2006 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Information Disclosure Statement

[6] With the exception of reference 4 (Foltmann et al.), all references cited in the IDS filed 31 October 2006 have been considered by the examiner. A copy of Form PTO/SB/08 is attached to this Office action. Reference 4 has been line through as the publication date of the reference, as required by 37 CFR 1.98(b)(5), is not provided.

Claim Rejections - 35 USC § 112, Second Paragraph

[7] Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

Claim 17 depends from claim 9, which has been amended to require a pH in the range of 1.0 to 1.8. Claim 17 is confusing and lacks antecedent basis in the recitation of "pH in the range of 1.0 to 1.99" as the recited pH range in claim 17 is broader than the claim from which it depends. It is suggested that applicant clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

[8] The written description rejection of claims 5-6, 9-14, 16-18, 35-36, 39, and 42-43 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the claims are limited to a method using a medium of a bacterial, yeast, or filamentous fungi organism that comprises a gene encoding chymosin that is "derived from" a bovine or *Camelidae* species. Applicant notes that the specification includes specific examples utilizing organisms comprising genes encoding chymosin derived from a bovine species and further notes that the specification "references camel chymosin," which has been made recombinantly. Applicant refers to example 2 of WO 2001/58924 and example 1 of WO

2002/36752 in support of the position that the invention was fully described at the time of filing.

Applicant's argument is not found persuasive. As noted in the prior Office action, the specification discloses that the claimed method can be applied to "a medium that is derived from the cultivation of a recombinant microorganism that has an inserted gene expressing the aspartic protease" (paragraph bridging pp. 7-8), that the claimed method is applicable to "preparations of aspartic proteases derived from naturally produced aspartic protease by addition or deletion of one or more amino acids or substituting one or more amino acids herein" (specification at p. 8, lines 32-35) and states that the term "aspartic protease" includes pro-chymosin and chymosin (p. 8, line 24). Thus, in accordance with MPEP § 2111.01, which directs the examiner to interpret claims as broadly as their terms allow, the examiner has interpreted "chymosin that is derived from a bovine or *Camelidae* species" in claim 9 as encompassing *any* mutant form of bovine or *Camelidae* chymosin.

As further noted in the prior Office action, the specification discloses only a single representative species of the recited genus of chymosin genes, i.e., bovine chymosin and fails to disclose the structures of any mutants of bovine chymosin that maintain the required 75% chymosin activity following pH treatment at a pH range of 1.0 to 1.8.

Also, while there is no dispute that the specification makes reference to camel chymosin in original claim 29 and at p. 8, lines 28-29 of the specification, the specification and prior art nonetheless fail to adequately describe the recited genus of genes encoding a *Camelidae* chymosin or any mutant forms thereof. According to

MPEP 2163.I, "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention" (citation omitted) and "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (citation omitted). In this case, other than describing the genus of genes encoding a *Camelidae* species chymosin by mere functional features, the specification and prior art fail to disclose any distinguishing identifying characteristics of a gene encoding *Camelidae* chymosin, *e.g.,* the nucleotide sequence of a gene encoding a *Camelidae* species chymosin, or a method for obtaining such gene. According to MPEP 2163.I.A, "[a] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes." In this case, there appears to be no known or disclosed correlation between the function of a *Camelidae* chymosin gene and its structure such that a skilled artisan would be able to recognize or visualize the members of the genus and distinguish them from others. While applicant attempts to rely on the disclosures of WO 2001/58924 and WO 2002/36752 to show possession at the time of filing, the disclosure of WO 2001/58924 fails to describe any distinguishing identifying characteristics of a

Camelidae chymosin gene and, while WO 2002/36752 discloses a method of obtaining a *Camelidae dromedarius* chymosin gene (Example 1, beginning at p. 18), this information is neither disclosed or made reference to in the instant application such that a skilled artisan would recognize that the inventor of the claimed invention was in possession of a *Camelidae* chymosin gene at the time of filing.

At least for the reasons noted above, it is the examiner's position that the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[9] The scope of enablement rejection of claims 5-6, 9-14, 16-18, 35-36, 39, and 42-43 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the claims are limited to a method using a medium of a bacterial, yeast, or filamentous fungi organism that comprises a gene encoding chymosin that is "derived from" a bovine or *Camelidae* species. Applicant notes that the specification includes specific examples utilizing organisms comprising genes encoding chymosin derived from a bovine species and further notes that the specification "references camel chymosin," which has been made recombinantly. Applicant refers to example 2 of WO 2001/58924 and example 1 of WO 2002/36752 in support of the position that the invention was fully described at the time of filing.

Applicant's argument is not found persuasive. As noted in the prior Office action, the specification discloses that the claimed method can be applied to "a medium that is derived from the cultivation of a recombinant microorganism that has an inserted gene expressing the aspartic protease" (paragraph bridging pp. 7-8), that the claimed method is applicable to "preparations of aspartic proteases derived from naturally produced aspartic protease by addition or deletion of one or more amino acids or substituting one or more amino acids herein" (specification at p. 8, lines 32-35) and states that the term "aspartic protease" includes pro-chymosin and chymosin (p. 8, line 24). Thus, in accordance with MPEP § 2111.01, which directs the examiner to interpret claims as broadly as their terms allow, the examiner has interpreted "chymosin that is derived from a bovine or *Camelidae* species" in claim 9 as encompassing *any* mutant form of bovine or *Camelidae* chymosin.

As further noted in the prior Office action, the specification discloses only a single working example of the recited chymosin genes, i.e., bovine chymosin and fails to disclose the structures of any mutants of bovine chymosin that maintain the required 75% chymosin activity following pH treatment at a pH in the range of 1.0 to 1.8.

Also, while there is no dispute that the specification makes reference to camel chymosin in original claim 29 and at p. 8, lines 28-29 of the specification, the specification and prior art nonetheless fail to enable the recited gene encoding a *Camelidae* chymosin or any mutant forms thereof as broadly encompassed by the claims. There is no disclosure of a nucleic acid encoding a *Camelidae* chymosin or mutant forms thereof or a method for obtaining such and while MPEP 2164.01, "[a]

patent need not teach, and preferably omits, what is well known in the art," there is no evidence of record that the prior art enabled a *Camelidae* chymosin gene. While applicant attempts to rely on the disclosures of WO 2001/58924 and WO 2002/36752 to show possession at the time of filing, the disclosure of WO 2001/58924 fails to enable a *Camelidae* chymosin gene and, while WO 2002/36752 discloses a method of obtaining a *Camelidae dromedarius* chymosin gene (Example 1, beginning at p. 18), this information is neither disclosed or made reference to in the instant application and there is no evidence of record that such information was available to a skilled artisan at the time of the invention ("[a]ny analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention," (emphasis added; MPEP 2164.01). As noted in MPEP 2164.01(b), The Court in *In re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available." In this case, the "apparatus," *i.e.,* the bacterial, yeast, or fungal organism comprising a gene encoding a *Camelidae* chymosin gene, does not appear to be readily available and the specification fails to provide a "sufficient disclosure of the apparatus." Consequently, the specification fails to enable a bacterial, yeast, or fungal organism comprising a gene encoding a *Camelidae* chymosin gene.

At least for the reasons noted above, it is the examiner's position that the specification fails to enable the full scope of the claimed invention without requiring undue experimentation.

Claim Rejections - 35 USC § 103

[10] The rejection of claim(s) 5-6, 9, 12-14, 16-18, and 42-43 under 35 U.S.C. 103(a) as being unpatentable over Ward et al. in view of Larsen et al. is withdrawn upon further consideration of the claims and in view of applicant's remarks.

Claim 9 has been amended to require a pH range of 1.0 to 1.8. According to MPEP 2143, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." The method of Ward et al. is practiced at a pH of 2.0 and, while Larsen et al. acknowledges that a pH of as low as 0.5 is suitable for chymosin activation, there is no teaching in the prior art of record that would provide motivation to practice the method of Ward et al. at a pH of 1.8. As such, the rejection is withdrawn.

[11] Claims 5-6, 9, 12-14, 16-18, and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawlis, Jr. et al. (US Patent 5,801,034) in view of Ward et al. (*Biotechnol* 8:435-440; cited in the IDS filed 16 April 2001). The rejection is necessitated by amendment to limit the pH range of claim 9 to 1.0 to 1.8.

The claims are drawn to a method for reducing glucoamylase activity in a milk clotting composition comprising the steps of: i) providing a medium having a pH of 2.0 or higher, wherein the medium comprises chymosin activity and glucoamylase activity and is derived from the cultivation of an organism selected from a bacterial species, a yeast species, and a species of filamentous fungi, wherein the organism comprises a gene encoding a chymosin derived from a bovine or *Camelidae* species; and ii) subjecting the medium to a pH in the range of 1.0 to 1.8 for a time sufficient to inactivate at least 50% of said glucoamylase activity while maintaining at least 75% of chymosin activity.

The reference of Lawlis, Jr. et al. teaches, "[i]n the various processes of culturing or fermenting microorganisms, it is sometimes necessary during or at the conclusion of the fermentation process to be able to kill the active cells in the mixture so that the desired product can be recovered from the culture or fermentation mixture. This is particularly true when microorganisms containing recombinant DNA are grown as production hosts and it is desirable to prevent any viable recombinant organisms from being released into the environment" (column 1, lines 18-25). Lawlis, Jr. et al. teaches, "[i]n the development of this invention, it has been found that the change in pH alone of a fermentation mixture does not accomplish a complete or substantially complete cell kill. For example, in a culture of *Asperaillus niger* for the production of chymosin, reducing the pH to about 2 using sulfuric acid does not accomplish a complete or substantially complete cell kill" (column 2, lines 58-64). According to Lawlis, Jr. et al., "[t]he process of this invention can be employed using any desired organic

acid following the above steps, provided the pH of the culture or fermentation mixture is first adjusted using a mineral acid to a pH approximately equal to or less than about 2 pH units below the pK.sub.a of the organic acid selected for use for the cell kill. For example, if formic acid (pK.sub.a =3.75) is to be used to accomplish the cell kill, the pH of the mixture will be adjusted with a mineral acid to about 1.75 or less, then formic acid is added to accomplish the cell kill" (column 3, lines 51-60). See also claim 1 of Lawlis, Jr. et al., which specifically recites the use of formic acid in the disclosed method. The working examples of Lawlis, Jr. et al., although using acetic acid and not formic acid, teach that "substantially complete cell kill" can be achieved by overnight incubation (Example 1), a 60 hour incubation (Example 2), and a 4 hour incubation (Example III). Lawlis, Jr. et al. does not teach practicing the method with a medium comprising chymosin and glucoamylase activities.

Ward et al. teaches the use of an expression vector in which the cDNA encoding bovine prochymosin B was fused in frame immediately following the codon for the last amino acid of *Aspergillus awamori* glucoamylase gene and recombinant production of chymosin in *A. awamori* transformed with this vector "led to the secretion of considerably higher amounts of chymosin than obtained with previous chymosin vectors" (p. 435, left column, abstract). See also p. 437, right column, Table 2. According to Ward et al., the *A. awamori* medium comprising the secreted fusion exhibited chymosin activity and glucoamylase activity (p. 437, right column, Table 2).

Therefore, at the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Lawlis, Jr. et al. and Ward et al. to

use a culture of the transformant of Ward et al. in the method of Lawlis, Jr. et al., namely, treating the culture with sulfuric acid to a pH of 1.75 and then adding formic acid to effect substantial cell kill. One would have been motivated to use the transformant of Ward et al. in the method of Lawlis, Jr. et al. because the transformant of Ward et al. produces "considerably higher amounts of chymosin." One would have had a reasonable expectation of success for using the culture of Ward et al. in the method of Lawlis, Jr. et al. because of the teachings of Lawlis, Jr. et al. and Ward et al. Therefore, claims 5-6, 9, 12-14, 16-18, and 42-43, drawn to the method as noted above would have been obvious to one of ordinary skill in the art at the time of the invention.

The following comments are provided to clarify the record. It is noted that Lawlis, Jr. et al. discloses, "[i]n a preferred embodiment...acetic acid is particularly useful in killing cells in fermentation processes" (column 4, lines 54-56). If applicant traverses the instant rejection on the ground that by acknowledging acetic acid as a preferred embodiment Lawlis, Jr. et al. teaches away from using formic acid, applicant's attention is directed to MPEP 2123.II, which states, "[d]isclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments" (citation omitted).

According to MPEP 2112, "[t]he express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. 'The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and Obviousness'" (citation omitted). MPEP 2112.IV states, "'To establish inherency, the extrinsic evidence must make clear that the missing descriptive

matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill" (citation omitted). While it is acknowledged that the combination of references fails to teach inactivation of at least 50% or 90% of the glucoamylase activity, while maintaining at least 75% or 85% of the chymosin activity, this would be an inherent characteristic of practicing the method of Lawlis, Jr. et al. with a culture medium of the transformant of Ward e al., particularly as Lawlis, Jr. et al. teaches treating a culture medium at a pH of 1.75 with overnight incubation or incubation for 4 hours, which pH and time are disclosed in the specification to achieve the desired reduction in glucoamylase activity while maintaining the desired level of chymosin activity. See particularly p. 7, lines 21-23, which discloses, "[t]ypically, however, the required treatment period is within the range of 0.1 minutes to 48 hours such as a range of 1 minute to 36 hours including the range of 10 minutes to 24 hours." See also the specification's working examples beginning at p. 9.

Further, while applicant argues that a skilled artisan would not expect a reduction in glucoamylase activity by practicing the method of the prior art, as noted above, such a reduction would be an inherent result of practicing the method suggested by the prior art. Also, it is noted that, in accordance with MPEP 2144, "[t]he reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant" (citation omitted).

At least for the reasons noted above, it is the examiner's position that the claimed invention would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

[12] Status of the claims:

- Claims 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 are pending.
- Claims 5-6, 9-14, 16-18, 29-31, 35-36, 39, and 42-43 are rejected.
- No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656